REMARKS

REJECTIONS UNDER §101 and §112, FIRST PARAGRAPH

The claims have been amended to recite that the polypeptides are "isolated." This amendment does not change the scope of the claims, since it would have been understood by the skilled worker that the claims as filed do not "read" on "naturally-occurring" (Office action, Page 3) polypeptides, especially read when read in light of the specification. See, e.g., Specification, Page 6, lines 8-13.

It is alleged in the Office action (beginning on Page 3) that the claimed polypeptides do not have a specific asserted utility.

As explained in the specification, the claimed polypeptides are coded for by nucleic acids which are overexpressed in ovarian tumor tissue and therefore can be used, e.g., as diagnostic markers and disease targets. See, e.g., Specification, Page 1; Page 4, lines 1-3; and Page 14. SEQ ID NO: 288 which is coded for by SEQ ID NO: 265 (Page 162) is shown on Page 130 and Page 159 as being expressed in higher levels in ovarian tumor tissue as compared to normal ovarian tissue. As indicated on Page 468 of the attached page from the *Molecular Biology of the Cell*, "transcription (transcriptional control) usually predominates" in "the pathway from RNA to protein," leading to the reasonable expectation that overexpression of the RNA would lead to overexpression of the corresponding protein. Thus, polypeptides of SEQ ID NO: 288 would be useful as diagnostic markers for ovarian cancer. This utility is adequate to meet the requirements of Section 101. See, e.g., *Utility Guidelines*, Pages 69-70, where a marker for cancer is described as having a well-established utility. These pages are attached for the examiner's convenience.

In further support of this, attached is a figure showing expression of the polypeptide corresponding to SEQ ID NO: 288 (also, known as "AGR2"). The photo on the left is of a section of a papillary ovary-adenocarcinoma. The tumor cells are stained red. The surrounding normal cells

are blue. The section was incubated with a primary rabbit antibody raised against AGR2 polypeptide, following by a secondary anti-rabbit antibody and streptavidin-coupled horseradish peroxidase. Staining was done with DAB as a chromogenic substrate (red) and hemalaun (blue). The negative control was a tissue section incubated with commercially available pre-immune rabbit serum, and then processed as above. The ovarian tumor cells expressed much higher amounts of AGR2 than the normal cells. These results clearly establish that, as expected, a polypeptide having the sequence of SEQ ID NO: 288, is overexpressed in an ovarian tumor.

It is also stated on Page 4 of the Office action there is no "factual evidence" that the polypeptides would be useful as a pharmaceutical agent. According to the M.P.E.P. 2107.02:

> In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101. See, e.g., In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); In re Irons, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); In re Langer, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); In re Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). As the Court of Customs and Patent Appeals stated in In re Langer:
>
> > As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.
>
> Thus, Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. See In re Langer, 503 F.2d at 1391, 183 USPQ at 297; In re Malachowski, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate.

The fact that polypeptides of SEQ ID NO: 288 are overexpressed in tumor cells provides a reasonable basis for their use as pharmaceutical agents, e.g., to generate antibodies *in vivo* to tumor tissue (i.e., vaccine immunotherapy). These are a number of antibody-based products that are in therapeutic use which are targeted at polypeptides expressed in tumor tissue, including, e.g., Herceptin® (Trastuzumab) and Rituxan® (Rituximab). Instead of the antibody, the target polypeptide can be administered to induce the antibodies *in situ* in the subject to be treated. Given the data showing overexpression of the polypeptide coupled with the state of the art, there is no scientific reason to doubt the validity of the assertion.

It would also be routine to select polypeptide sequences which are "specific fragments" of SEQ ID NO 268. See, e.g., Claim 50. The phrase "specific fragment" indicates that the fragments are characteristic ("specific") of SEQ ID NO: 268. While this phrase is not expressly recited in the specification, it would be understood by the skilled worker that applicant was in possession of it. See, e.g., Specification, Page 6, lines 21-23. "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in ipsis verbis [i.e., "in the same words"] to be sufficient")." M.P.E.P. §2163. Specific fragments could be selected routinely, e.g., by identifying sequences in SEQ ID NO: 268 which are present in it, but no other sequence. This can be accomplished, e.g., by polypeptide searching using BLAST and other conventional search algorithms.

Similarly, sequences having at least 90% homology could be routinely identified and manufactured by the skilled worker. Claim 45 indicates that such sequence is "human," i.e., identified in human tissue. Thus, for example, naturally-occurring allelic variants and polymorphisms of SEQ ID NO: 268 could be identified in human tissues using conventional

methods. Furthermore, claim 49 also indicates that the polypeptide is overexpressed in ovarian tissue.

REJECTION UNDER §112, SECOND PARAGRAPH

Claims 24 and 35 are not indefinite in the recitation of the group of claimed sequences. For example, they are overexpressed in ovarian tumor tissue. The objection rejection of these claims is not understood.

The phrase "at least 80% homology" is alleged to be unclear "because the recitation encompasses undisclosed limit of the percentage of homology." The phrase would be understood by the skilled worker to have an upper limit of 100%, i.e., when the two sequences are perfectly homologous or identical.

Claim 27 has been amended to clarify the claim. Such amendments were unnecessary since its meaning would have been plain to the skilled worker, e.g., when read in light of the specification.

REJECTION UNDER §102

Claim 25 has been cancelled without prejudice, rendering the rejection of it moot. This is not an acquiescence to the rejection, but is merely to expedite allowance of the pending claims.

PROVISIONAL REJECTIONS

Applicants will address any rejection over claims in related applications, upon notice that the pending claims are allowable.

INFORMATION DISCLOSURE STATEMENT

Applicants respectfully request the Examiner to initial the second page of the PTO-1449 Form. Copy attached.

CONCLUSION

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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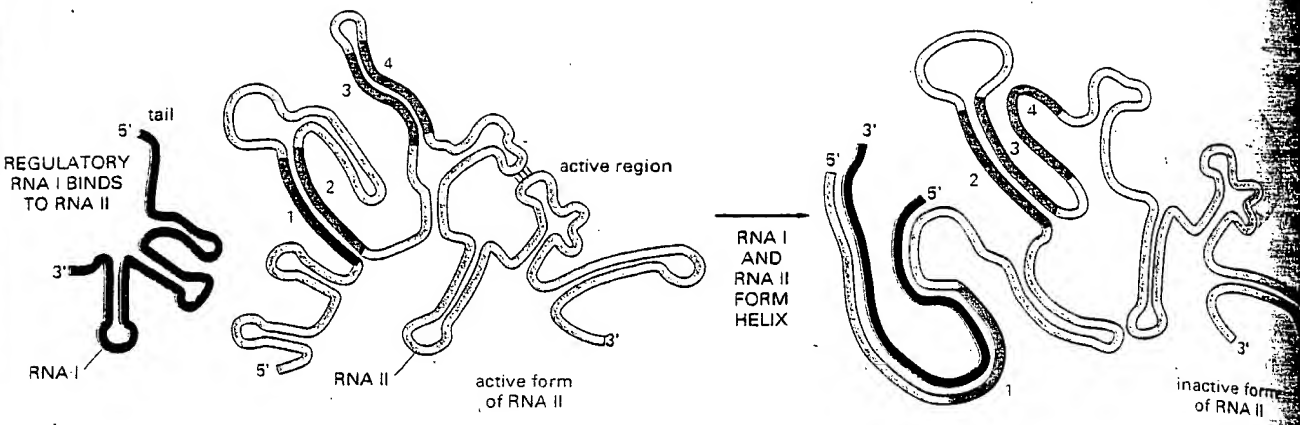

Figure 9–89 Antisense RNA strate... for regulating plasmid numbers... bacteria. A regulatory interaction... between two RNA molecules maintains a constant plasmid cop... number in the ColE1 family of bacterial DNA plasmids. RNA I (abo... 100 nucleotides long) is a regulatory... RNA that inhibits the activity of RNA... II (about 500 nucleotides long), whic... normally helps initiate plasmid DNA... replication. The concentration of RNA... I increases in proportion to the number of plasmid DNA molecules in the cell, so that as plasmid numbers increase, plasmid replication is inhibited. RNA I is complementary in sequence to the 5′ end of RNA II. In RNA II sequence 2 is complementary to both sequence 1 and sequence 3, and it is displaced from one to the other by the binding of RNA I; RNA I thereby alters the conformation of sequence 4, inactivating RNA II. (After H. Masukata and J. Tomizawa, *Cell* 44:125–136, 1986.)

accomplished by specialized RNA-binding proteins. In other cases, however, the recognition of specific RNA sequences is carried out by other RNA molecules, which use complementary RNA-RNA base-pairing as part of their recognition mechanism. RNA-RNA pairings, for example, are known to play a central part in translation, in RNA splicing, in several other forms of RNA processing, and in the RNA editing that occurs in trypanosomes. In attempting to dissect posttranscriptional mechanisms, we have largely entered an RNA world.

RNA molecules also have other regulatory roles in cells. The *antisense RNA* strategy for experimentally manipulating cells so that they fail to express a particular gene (see p. 326) mimics a normal mechanism that is known to regulate the expression of a few selected genes in bacteria and may be used much more widely than is now realized. A well-understood example of this kind of mechanism provides a feedback control on the initiation of DNA replication for a large family of bacterial DNA plasmids. The control system limits the number of copies of the plasmid made in the cell, thereby preventing the plasmid from killing its host cell by overreplicating (Figure 9–89).

Studies of RNA-catalyzed reactions are of special interest from an evolutionary perspective. As discussed in Chapter 1, the first cells are thought to have lacked DNA and may have contained very few, if any, proteins. Many of the RNA-catalyzed reactions in present-day cells seem to represent molecular fossils—descendants of the complex network of RNA-mediated reactions that are presumed to have dominated cell metabolism more than 3.5 billion years ago. Recombinant DNA technology has allowed large amounts of pure RNAs of any sequence to be produced *in vitro* with purified RNA polymerases (see Figure 7–36), making it possible to study the detailed chemistry of RNA-catalyzed reactions. From an understanding of many such reactions, biologists hope to be able to trace the path by which a living cell first evolved.

Summary

Many steps in the pathway from RNA to protein are regulated by cells to control gene expression. Most genes are thought to be regulated at multiple levels, although control of the initiation of transcription (transcriptional control) usually predominates. Some genes, however, are transcribed at a constant level and turned on and off solely by posttranscriptional regulatory processes. These processes include (1) attenuation of the RNA transcript by its premature termination, (2) alternative RNA splice-site selection, (3) control of 3′-end formation by cleavage and poly-A addition, (4) control of transport from the nucleus to the cytosol, (5) localization of mRNAs to particular parts of the cell, (6) RNA editing, (7) control of translational initiation, (8) regulated mRNA degradation, and (9) translational recoding. Most of these control processes require the recognition of specific sequences or structures in the RNA molecule being regulated. This recognition can be accomplished by either a regulatory protein or a regulatory RNA molecule.

References

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Front cover: The photograph shows a rat nerve cell in culture. It is labeled (*yellow*) with a fluorescent antibody that stains its cell body and dendritic processes. Nerve terminals (*green*) from other neurons (not visible), which have made synapses on the cell, are labeled with a different antibody. (Courtesy of Olaf Mundigl and Pietro de Camilli.)

Dedication page: Gavin Borden, late president of Garland Publishing, weathered in during his mid-1980s climb near Mount McKinley with MBoC author Bruce Alberts and famous mountaineer guide Mugs Stump (1940–1992).

Back cover: The authors, in alphabetical order, crossing Abbey Road in London on their way to lunch. Much of this third edition was written in a house just around the corner. (Photograph by Richard Olivier.)

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS

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3) Is the asserted utility specific? The answer to this question is yes. In this case, the monoclonal antibody is specific for a specific protein, namely receptor A. Therefore, there is an asserted specific utility for the claimed invention.

4) Is the asserted utility substantial? The answer to this question is no. Specifically, since neither the specification nor the art of record disclose any diseases or conditions associated with receptor A, the asserted utility in this case is a method of treating an unspecified, undisclosed disease or condition, which does not define a "real world" context of use. Treating an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. *See Brenner v. Manson*, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Thus, both a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should be made on claim 3.

Caveat:

Let us assume for the moment that the specification also discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. Assume also that the examiner has found and made of record a journal article published prior to the

application's filing date indicating that it is desirable to selectively detect melanoma cells as opposed to normal skin cells so as to diagnose that type of cancer. Does this change the above analysis?

For each of the claims, the above analysis changes right from the first question: Based on the record, is there a "well established utility" for the claimed invention? The answer to this question would change to yes in each case. Specifically, based on this record, there is a "well established utility" for the products of claims 1 and 3. The "well established utility" for the receptor A is a method of assaying for materials that bind to receptor A by contacting the materials to a complex of receptor A and protein X. Furthermore, making a monoclonal antibody to receptor A for diagnosing melanoma would constitute a well-established utility. Such utilities are "well established" because the disclosure of the properties of the receptor and antibody taken together with the knowledge of one skilled in the art indicates that these specific, substantial and credible utilities were known. With respect to claim 2, since there is now evidence of record providing a correlation between this method and diagnosing melanoma, i.e., materials identified by the method, such as the monoclonal antibody, can be used to diagnose melanoma, this method now has a "well established utility".

Therefore, utility rejections under 35 U.S.C § 101 rejection and a 35 U.S.C. § 112, first paragraph, should not be made against claims 1-3.